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Brief report
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Adolescent Smoking Cessation With Bupropion: The Role of Adherence

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Abstract

Introduction: While many medications can be effective aids to quitting tobacco, real world adherence to smoking cessation medications may render a potentially effective medication ineffective. The present study investigated the role of adherence on treatment outcomes in a bupropion dose-response study among adolescent smokers trying to quit smoking.

Methods: Three hundred twelve adolescent boys (n = 143) and girls (n = 169) between the ages of 14–17 were enrolled in the study, and were randomly assigned to use either 300 mg, 150 mg or placebo bupropion to quit smoking. Among the eligibility criterion, participants had to smoke at least six cigarettes per day, be motivated to quit smoking (self report), have an exhaled carbon monoxide level greater than or equal to 10 ppm, and report at least two previous quit attempts. Adherence to medication was determined by both self-report and actual counts of unused medication and empty medication packaging. Smoking status was determined by a combination of self-report and biochemical verification (breath carbon monoxide and urine cotinine).

Results: Cotinine-confirmed quit rates were significantly higher as a function of high adherence (20.69%) relative to low adherence (0.00%) in the 300-mg Bupropion Sustained Release group. Overall adherence in all study conditions in this highly controlled study was high (74%), but was significantly lower in non-white participants.

Conclusions: Effectiveness of bupropion for adolescent smoking cessation is contingent on achieving high rates of medication adherence, but considerable variations in adherence impacted outcomes.

Implications: Few studies have assessed the safety and efficacy of medications to help adolescent smokers quit, and we conducted one such study assessing bupropion. In this analysis of that original study, we assess the role of adherence in use of medication and quit rates. We found that adherence was related to outcomes, particularly in the 300-mg dose of bupropion.

Introduction

Evidence suggests that most young smokers want to quit; yet several studies indicate that only a small percentage (in the range of about 12%–16%) of those who want to quit succeed.[1,2] In the latest review of 64 adolescent tobacco use cessation studies, Sussman and Sun[1] found mixed support for pharmacologic treatment for youth smokers. However, only three of the 13 published studies include specific data about adolescents' adherence to the pharmacologic treatment, and none of the studies explored in depth the relationship between adherence and treatment outcomes.

In this article, we report on the relationship between adherence and treatment outcomes in a study assessing bupropion for adolescent smoking cessation. Adherence data are derived from our published research,[3] and a brief summary of the published protocol is as follows: 312 adolescent boys (n = 143) and girls (n = 169) participated in a prospective, randomized, placebo-controlled, dose-ranging clinical trial (FDA Phase III) of sustained release (SR) bupropion for smoking cessation with a medication treatment period of 6 weeks with follow-up through 26 weeks post-enrollment. The primary study goal was to determine the efficacy and safety of two doses of bupropion (150 mg and 300 mg) in comparison with placebo. Self-reported abstinence was verified by exhaled breath carbon monoxide (CO) less than 10 ppm at each visit and urine cotinine level less than or equal to 50 µg/L at weeks 2 and 6. We found that the 300-mg dose resulted in significantly higher quit rates at the end of the 6-week treatment period.

To assess whether adherence played a role in the efficacy of bupropion, we explored the following specific research questions: To what extent were participants in the study adherent to the treatment regimen? What impacted treatment adherence? Did adherence impact treatment outcomes differentially across study conditions?

Methods

In this further analysis of data from our study on bupropion, we completed an in-depth analysis of adherence and its relationship to treatment outcomes and adverse events. Toward that end, we assessed the following measures:

Adherence: Boys and girls were seen weekly for 6 weeks after receiving medications. At each appointment, participants returned unused medication in its original blister pack, received the next 10-day supply of medication and brief behavioral counseling. During each session, the study case manager tracked doses taken by conducting a count of undisturbed pills in each blister pack and recorded the data in the participant's case report form. Participants were also asked to explain the reasons for any missed doses. For all randomized participants, percent adherence was calculated by dividing the number of doses reported taken by the total 6-week regimen (95 doses). Participants were categorized into "highly adherent" if they took at least 80% of the prescribed regimen and "low adherent" if they did not meet the highly adherent criterion.

Abstinence: The primary outcome measure was biochemically confirmed abstinence from smoking at week 6, defined as self-report of not smoking any part of a cigarette in the week prior to the visit (7-day point prevalence), breath CO less than 10 ppm, and urine cotinine level less than or equal to 50 µg/L. This primary outcome measurement is the recommended standard in the smoking cessation literature for both adult[4] and youth.[5]

Smoking Characteristics: Secondary measures of smoking included smoking history, which assessed age of smoking onset, cessation history, and smoking pattern in the past 3 months. Nicotine dependence was also determined using the modified Fagerström Tolerance Questionnaire which has been validated with adolescent respondents.[6] At weekly visits, symptoms of smoking withdrawal were assessed via eight questions scaled to assess severity of the symptoms.[3]

Analytic Methods

Study drug adherence in the clinical trial was used as an assessment of treatment adherence. Two variables were used to assess treatment adherence and included as predictors of abstinence in regression models. The first was a binary variable which categorized participants as "highly adherent" if they completed at least 80% and "low adherent" if they competed less than 80% of the prescribed regimen.[7] The second measure of treatment adherence was a continuous variable of the percentage of prescribed regimen taken. The outcome measures, abstinence at week 2 and week 6, were included as binary variables in the regression models.

One-way analysis of variance was used to test differences in adherence rates across treatment groups and by abstinence status. Further testing using Pearson's χ^2 test or a Fisher's Exact test, with a Bonferonni correction ($P \leq .05/6$ tests = .0062), was implemented to identify significance differences in each group.

Multiple logistic regression was used to examine the relationship between adherence, treatment group (dose) and abstinence, and multiple linear regression was used to predict percent adherence. A selection-based approach was used to determine predictors. We examined basic descriptive statistics for each potential predictor (eg, amount of medication used) and reviewed for collinearity. A backward-based selection approach was used to determine the final model with the best fit. Model diagnostics included: Hosmer-Lemeshow's goodness of fit, deviance over dispersion graphic, index plots of influence, and a Receiver Operating Characteristic Curve graph to look at the accuracy of prediction.

We conducted a sensitivity analysis to investigate the role of missing data on the regression models. There were missing data on adherence measures for n = 10 who were not CO-confirmed abstinent at week 6. There were missing data for smoking status for n = 2 highly adherent and n = 2 low adherent participants. We found no statistical differences at baseline in those missing these data and those who were not for: gender, race, categories of number of cigarettes per day, and a categorical response of Fagerström scores.

When missing abstinence outcomes and missing adherence outcomes were imputed to be non-abstinent and low or no adherence, respectively, the magnitude of the coefficients increased. Therefore, we chose to show the analysis of completed cases, which was a more conservative approach.

Results

The overall adherence rate defined by percent of medication used was 74.24% (*SD* 26.79). Adherence rates did not differ across treatment groups (F = 0.29, P = .75). In addition, adherence rates did not differ across treatment groups in the highly adherent (91.00%, *SD* 6.13%) or low adherent (48.12%, *SD* 25.66%) groups. Adherence varied considerably, particularly in the low adherence group. As expected, there was a significant difference in medication use between those who were in the high and low adherence groups (F = 472.34, P = .00).

Adherence rates differed in those who were abstinent from smoking (CO-confirmed 7-day point prevalence) at week 6. Among all randomized participants, 65.93% of those who were highly adherent were abstinent from smoking, compared to 33.62% of those who were not highly adherent. In the 150-mg Bupropion SR group, 65.00% of those who were highly adherent were abstinent compared to 34.21% in the low adherent group. In the 300-mg Bupropion SR group, 77.42% of those who were highly adherent were abstinent compared to 27.03% abstinence in the low adherent group. When using the cotinine-confirmed 7-day point prevalence smoking abstinence measure, we found a statistically significant difference in

Table 1. 7-Day Point Prevalence Abstinence at Week 6 by Adherence, *n* (% Down Columns)

	All randomized		Placebo		150-mg Bupropion SR		300-mg Bupropion SR	
	Highly adherent	Low adherent	Highly adherent	Low adherent	Highly adherent	Low adherent	Highly adherent	Low adherent
CO confirmed								
Abstinent	**120 (65.93)**	**39 (33.62)**	33 (55.00)	16 (39.02)	**39 (65.00)**	**13 (34.21)**	**48 (77.42)**	**10 (27.03)**
Not abstinent	**62 (34.07)**	**77 (66.38)**	27 (45.00)	25 (60.98)	**21 (35.00)**	**25 (65.79)**	**14 (22.58)**	**27 (72.97)**
Cotinine confirmed								
Abstinent	**24 (13.48)**	**5 (4.39)**	3 (5.08)	2 (5.00)	9 (14.75)	3 (8.11)	**12 (20.69)**	**0 (0.00)**
Not abstinent	**154 (86.52)**	**109 (95.61)**	56 (94.92)	38 (95.00)	52 (85.25)	34 (91.89)	**46 (79.31)**	**37 (100.00)**

CO = carbon monoxide; SR = Sustained Release. Bolded results have a statistically significant test or a Fisher's Exact test.

the highly adherent group (13.48% abstinent) compared to the low adherent group (4.39% abstinent) at week 6 (Table 1).

In addition, there is a statistically significant difference in quit rates as a function of high and low adherence in the 300-mg Bupropion SR group whose abstinence was cotinine confirmed: 20.69% of those who are highly adherent were abstinent at week 6 compared to 0.00% of those who are low adherent. Neither the placebo nor the 150-mg Bupropion SR group showed significant differences when using cotinine verified abstinence. We found no statistical differences at baseline in those missing these data and those who were not for: gender, race, categories of number of cigarettes per day and a categorical response of Fagerström scores.

Logistic regression models were conducted to look at the relationship between adherence and cessation. Those who were highly adherent were 3.35 times ($z = 4.91$, $P \leq .00$) more likely to be CO-confirmed abstinent at week 2, 3.82 times ($z = 5.34$, $P \leq .00$) more likely to be CO-confirmed abstinent at week 6, and 3.40 times ($z = 2.14$, $P \leq .02$) more likely to be cotinine-confirmed abstinent at week 6 than those who had low adherence. The multiple logistic regression that included treatment group revealed that those who were highly adherent and on 300-mg Bupropion SR were 4.85 times ($z = 2.50$, $P \leq .01$) more likely to be CO-confirmed abstinent at week 6 than those with low adherence, but high or low adherence was not related to treatment outcome in those taking 150-mg Bupropion SR.

Multiple linear regression was employed to examine predictors of adherence, using the continuous measure of percent adherence. There were four statistically significant predictors of adherence. While holding all other covariates constant, (1) those who were a race other than white/Caucasian were 8.0% less adherent, (2) those who were abstinent at week 2 were 12.0% more adherent, (3) those who were abstinent at week 6 were 12.8% more adherent, and (4) those who permanently discontinued medications due to adverse events were 57.7% less adherent (which was an expected result). Adherence was not related to total number of adverse events or adverse events of severe intensity.

Discussion

In summary, overall mean adherence across all participants was 74%, which is considerably higher than that found in other adolescent treatment trials, but there was considerable individual variability, particularly in those with low adherence, despite no differences in adherence between the three treatment conditions. Across all treatment groups, 65% of those who were highly adherent were CO-verified abstinent versus 36% of those with low adherence, and this pattern was sustained but at a lower level of abstinence when adherence was verified by cotinine (13.5% vs. 4.9%, respectively). This latter result was driven largely by highly adherent participants in the 300-mg condition, who were significantly more likely to be abstinent (cotinine verified) than the low adherent participants (20.7% vs. 0.0%, respectively). In short, those with low adherence in any treatment condition were least likely to become abstinent.

Medication adherence was the same across treatment conditions, which suggests that any medication effects were more likely due to the medication itself rather than other potential factors (eg, motivation). In addition, comparability in adherence across conditions suggests that efforts to educate on proper medication usage increased adherence. The relatively high overall adherence suggests that all participants were likely highly motivated, particularly because their parents had to sign a consent form for their participation and they had to sign an assent form. Thus, generalizability to broader populations of adolescent smokers is uncertain.

As with our research on adult adherence to varenicline for smoking cessation, we found that abstinence at week 2 was a significant predictor of high adherence.[7] Unlike our varenicline study; however, the current study found that abstinence at week 6 was also related to high adherence. It is very possible that our extensive screening process resulted in only the most highly motivated and skilled making it into the study.

The results of this study have significant relevance to the treatment of adolescent smokers, which remains a very under-investigated area. These results affirm that adherence is critically important for the FDA-approved dosage of bupropion (300 mg) to be effective in helping adolescents to quit smoking—particularly ethnic minorities since their adherence was lower than white participants. Those treating tobacco dependence must implement methods to assure that youth will use their bupropion as recommended.

Several additional limitations of the present study exist, and limit generalizability. This study was very highly controlled, and study participants were screened to decrease the chances that low-motivated smokers and those with other medical conditions could participate. Because the study was so highly controlled, adherence rates are almost certainly higher overall than would be seen in real world use. In addition, now that a SR version of bupropion is now available as a once-a-day dose, real world adherence is likely to be greater than the dosing options when the study was implemented. In addition, we observed very large differences in quit rates as determined by breath CO and cotinine. While the trends are consistent between breath CO and cotinine, our finding of considerably lower abstinence as determined by cotinine suggests youth in the study may have refrained from or reduced smoking immediately before coming to the clinic to appear abstinent, which was important for many of them because it

was clear that there parents strongly encouraged them to quit smoking. Furthermore, we do not know for certain if high adherence lead to increased quit rates, or whether those not experiencing beneficial medication effects became less adherent, but the overall high adherence rates across treatment conditions suggests adherence the former explanation. However, this question requires further research. Finally, though this study is one of the largest to investigate adolescent smoking cessation, it is far too small to be sure results involving subject subpopulations or negative results are accurate.

Despite the study limitations, the results of this study reinforce what we know from adult smoking cessation studies: adherence is essential to treatment success. Far more research is needed to enhance treatment adherence in both adolescents and adults seeking treatment for tobacco dependence, but in the meantime it is important that clinicians assess and treat adolescent smokers, and make every effort to assure adherence to the prescribed treatment by arranging follow-up with adolescent smokers to assess and address any obstacles to adherence.

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Declaration of Interests

SJL has served as a paid consultant to or conducted research for Pfizer, GSK, Cypress BioScience, and McNeil Consumer, and an unpaid consultant to NJOY, Inc and eNicotine Technology. MM, EM, LF, and RG have no declarations of conflict. McNeil Consumer is collaborating with GSK on a current study on nicotine replacement being conducted by Dr Leischow, and GSK markets bupropion.

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SJL and MM have contributed equally to this article.

References

1. Sussman S, Sun P. Youth tobacco use cessation: 2008 update. *Tob Induc Dis*. 2009;5(1):3. doi:10.1186/1617-9625-5-3.
2. Zhu SH, Sun J, Billings SC, Choi WS, Malarcher A. Predictors of smoking cessation in U.S. adolescents. *Am J Prev Med*. 1999;16(3):202–207.
3. Muramoto ML, Leischow SJ, Sherrill D, Matthews E, Strayer LJ. Randomized, double-blind, placebo-controlled trial of 2 dosages of sustained-release bupropion for adolescent smoking cessation. *Arch Pediatr Adolesc Med*. 2007;161(11):1068–1074.
4. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction*. 2005;100(3):299–303.
5. Mermelstein R, Colby SM, Patten C, et al. Methodological issues in measuring treatment outcome in adolescent smoking cessation studies. *Nicotine Tob Res*. 2002;4(4):395–403.
6. Prokhorov AV, Pallonen UE, Fava JL, Ding L, Niaura R. Measuring nicotine dependence among high-risk adolescent smokers. *Addict Behav*. 1996;21(1):117–127.
7. Hays JT, Leischow SJ, Lawrence D, Lee TC. Adherence to treatment for tobacco dependence: association with smoking abstinence and predictors of adherence. *Nicotine Tob Res*. 2010;12(6):574–581. doi:10.1093/ntr/ntq047.